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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,557	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *March 27, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *8-12,14,17-19,21,22 and 24-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,13,15,16,20 and 23* is/are rejected.

7)☒ Claim(s) *13, 15-16, 20 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 December 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on March 27, 2007 is acknowledged. The Examiner appreciates the telephone conversation with Applicant's representative on May 9, 2007 regarding the species election (v) listed below.

Applicant has elected the invention of Group I, claims 1-13 and 15-32, drawn to a method of identifying one or more agents with therapeutic activity to treat one or more symptoms of a disease which is associate with aberrant expression or activity of epithelial sodium channels (ENaC),

Within Group I, Applicant has further elected the restricted subgroup "IA", Claims 1-9, 13, 15-23 and 28-32, drawn to a method of identifying an agent with dual therapeutic activity in mammalian cells.

Within Group IA, Applicant has elected the following species:

i) the physiological agent category, antibiotic, as recited in Claim 16,

ii) the physiological agent compound , doxil, as recited in Claim 20. Upon further examination of the subject matter, the Examiner has extended the species to include doxorubicin.

iii) the cellular functionality, wherein the agent modulates transcription of a molecule that regulates ENaC transcription, as recited in Claim 23,

iv) the virus type, adeno-associated virus, as recited in Claim 4,

v) the selected transcriptional agent activity, wherein the agent is effective to decrease the level or amount of transcription of one or more subunits of ENaC, as recited in Claim 7, and

vi) the mammalian cell type species, human, as recited in Claim 15.

2. Election of Applicant's invention(s) was made with traverse.

With respect to the restriction between inventions, Applicant argues that:

a) the inventions are closely related,

b) the restriction requirement is optional,

c) Applicant should not be required to incur the additional costs associated with the filing of multiple divisional applications in order to obtain protection for the claimed subject matter, and

d) the claims of both Group IA and Group IB can be efficiently searched in a single search because those claims are classified in the same class.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), the Examiner has explained in the Requirement for Restriction why the inventions are distinct. The argument of close relatedness does not provide evidence of non-distinct inventions.

With respect to b), while requiring restriction is optional, the restriction has been required, and thus this ground of traversal is moot.

With respect to c), the cost of filing divisional applications on distinct inventions is not grounds for rejoinder of distinct inventions.

With respect to d), the Examiner has explained in the Requirement for Restriction why there would be a search and examination burden to examine all of the claimed inventions.

With respect to the species election requirements, Applicant argues that:

a) many of the species elections do not take into consideration the claimed invention, and so are improper, and

b) the species have a disclosed relationship.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), MPEP §803 states that "If the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits, even though they include claims to independent or distinct inventions." The Examiner has explained in the Requirement for Restriction why the species are independent and mutually exclusive of each other, and why one species would not necessarily render obvious other species.

With respect to b), it is noted that should Applicant traverse the species election requirement, that Applicant was invited to submit evidence or identify such evidence now of

record showing the species to be obvious variants or clearly admit on the record that this is the case. Applicant has not done so.

The requirement is still deemed proper and is therefore made FINAL.

Amendments

In the reply filed March 27, 2007, Applicant has amended Claims 14 and 53.

3. Claims 8-12, 14, 17-19, 21-22, and 24-53 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

4. Claims 1-7, 13, 15-16, 20 and 23 are under consideration.

Priority

5. Applicant's claim for the benefit of a prior-filed application parent provisional applications 60/459,323, filed March 31, 2003 and 60/512,347, filed October 16, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on January 17, 2006 and April 27, 2006, providing more than 230 references. The Examiner was able to consider these to the extent of time allowable and requests the Applicant to distinctly identify by page and line number with a concise explanation of relevance any statements within a citation directly applicable to the instantly claimed invention. The signed and initialed PTO Forms 1449 are mailed with this action.

Oath/Declaration

The oath or declaration filed December 1, 2004 is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

A) It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

B) It does not identify the citizenship of each inventor.

C) It was not executed in accordance with either 37 CFR 1.66 or 1.68.

D) Applicant has not given a post office address anywhere in the application papers as required by 37 CFR 1.33(a), which was in effect at the time of filing of the oath or declaration. A statement over applicant's signature providing a complete post office address is required.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Figure 11C, filed on December 1, 2004, does not reproduce well, and is essentially opaque. Thus, the Examiner is prohibited from evaluating the data on its merits. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

6. **The disclosure is objected to because of the following informalities**:

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: The specification uses the terms "doxorubicin", "doxyrubicin" and "doxil", each of which may be abbreviated as "DOX". However, the specification discloses that doxil could not be confirmed to be bioavailable to cell culture cells (pg 71, lines 22-24), and that "intranasally doxil-treated mice did better than the doxorubicin-treated animals" (pg 101, lines 7-9). Thus, one of ordinary skill in the art would reasonably conclude that the functional ability(ies) of "doxorubicin", "doxyrubicin" and "doxil", are not identical in effect. As such, it is imperative that "doxorubicin", "doxyrubicin" and "doxil", and use thereof, be clearly and explicitly identified throughout the disclosure.

A) The use of trademark compositions has been noted in this application. Doxil (pg 13, line 2) is a registered trademark name, DOXIL®, and represents a liposomal formulation of doxorubicin. Similarly, the specification uses the terms "Velcade" (pg 28, line 12), "Norvir, Kaletra, and Viracept" (pg 70, line 25), "Dowanol" and "Miglyol" (pg 43, lines 19-21) which are also registered trademarks. Trademarked compositions should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Applicant is advised to review the specification to correctly identify all trademark compositions.

B) The units (DF* and mU) categorizing the results in Table 2 (pgs 75-76) are not defined in the table or disclosed in the working example that describes the experiment used to acquire the data (Example 3), thus prohibiting a meaningful evaluation on the merits.

C) Figure 2 consists of two panels, A-B. However, the specification does not disclose the data present in its corresponding panel or the identity of the "RLU" units by which the data is measured and graphed (pg 13, lines 1-3).

D) The specification does not adequately identify the "DOX" compound whose effects are graphed in Figures 5-10 (pgs 13-15).

E) It appears that a typographical error has occurred regarding the citation of Stutts et al (pg 1, line 24).

Appropriate correction is required.

Claim Objections

7. **Claims 13, 15-16, 20 and 23 are objected to under 37 CFR 1.75(c)** as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. Furthermore, the claims recite dependency on claims (Claims 10, 11 and 12) drawn to non-elected inventions. See MPEP § 608.01(n).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. **Claims 1-7, 13, 15-16, 20 and 23 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The breadth of the claims is exceptionally large for encompassing an enormous genus of undefined symptoms of an enormous genus of etiologically and pathologically distinct diseases associated with aberrant expression or activity of an epithelial sodium channel, wherein the quantitative values by which an artisan would know *a priori* that the expression or activity of the enormous genus of epithelial sodium channels are "aberrant" is neither defined nor disclosed, and wherein the enormous genus of diseases have an undefined relationship to the enormous genus of epithelial sodium channels extant in an enormous genus of mammalian organisms, wherein the step of contacting the mammalian cells may be performed *in vitro*, *ex vivo* or *in vivo*.

The specification does not define the term "mammal", but discloses a preferred mammalian embodiment that is human (pg 4, lines 1-4). The art recognizes mammals to reasonably encompass some 5,500 species (including Humans), distributed in about 1,200 genera, 152 families and up to 46 orders (en.wikipedia.org/wiki/Mammal, last visited March 21,

2007). The art also recognizes that the mammalian body consists of a large genus of distinctly different organs, e.g. heart, lung, brain, muscle, skin, liver, etc.., and an even larger genus of distinctly different cell types. Thus, the claimed inventions reasonably embrace any mammalian cell type that endogenously possesses, or is transformed with a nucleic acid encoding (pg 4, lines 7-8), an epithelial sodium channel.

It is noted that the etiology and pathology of the claimed disease symptoms do not actually require that the one or more disease symptoms be caused by aberrant expression or activity of ENaC. Rather, the broadest reasonable interpretation is that the enormous genus of disease states present at least one symptom that has also been observed in those patients having aberrant ENaC expression or activity.

The claims are also broad for encompassing an enormous genus of distinctly different physical, chemical and cell biological processes that may be affected by an agent so as to enhance the "efficacy" of an enormous genus of structurally and functionally distinct gene therapy vectors, wherein the term "efficacy" is not defined.

The claimed inventions are directed to methods for identifying one or more agents with dual therapeutic activity. At issue for the purpose of enablement requirements, are:

a) the method step of selecting an agent identified only by it's *a priori* ability to inhibit or treat one or more symptoms of a disease which is associated with aberrant expression or activity of epithelial sodium channels, and

b) the method step of selecting an agent identified only by it's *a priori* ability to enhance the efficacy of a gene therapy vector in mammalian cells,

The State of the Prior Art

Epithelial Sodium Channels

The specification does not define the term "epithelial sodium channels", and thus the claimed subject matter reasonably embraces any sodium channel expressed in epithelial cells. In the absence of a definition, the specification discloses prior art to identify the claimed subject matter (pg 1, line 24; Stutts et al, J. Biol. Chem. 272(22):14037-14040, 1997; Donaldson et al, J.

Biol. Chem. 277(10):8338-8345, 2002 *of record), wherein the art teaches that ENaC is an acronym for amiloride-sensitive epithelial sodium channel, comprising α, β and γ subunits (pg 14037). However, the claimed genus of epithelial sodium channels reasonably embraces sodium channels neither disclosed nor contemplated by Applicant. For example, Schaefer et al and Sakai et al (FEBS Letters 471:205-210, 2000; J. Physiol 519:323-333, 1999) teach the identification of a novel amiloride-sensitive cation channel 5 that is expressed in the epithelia of the small intestine.

The art teaches that epithelial sodium channel (ENaC; found in databanks under SCA, for "sodium channel, amiloride-sensitive, and SCNN1, "sodium channel, non-neuronal) is a class of ion channels that was discovered at the beginning of the 1990s (Kellenberger et al, Physiological Review 82:735-767, 2002; gp 735-736, joining ¶). The first draft sequence of the human genome reveals the presence of α-, β-, γ- and δ-ENaC proteins (pg 737, col. 2, ¶1). ENaC is expressed in the kidney, colon, lung, and salivary gland (pg 737, col. 2). In mammals, the three ENaC subunits (α, β, γ) are expressed in keratinocytes of all epidermal layers (pg 739, col. 2, ¶3). ENaC transcripts can also be found in the pluristratified epithelium of the esophagus where ENaC's role is unknown. The expression of ENaC subunits along the respiratory epithelium is complex and varies between species (pg 739, col. 1, Lungs). Finally, salt taste is transduced by direct amiloride-sensitive influx of Na+ in the taste cells of the fungiform papillae of the anterior part of the tongue, suggesting the presence of an amiloride-sensitive Na+ channel (pg 739, col. 2, ¶4); however, the specific role of ENaC in salty taste transduction still remains to be clearly demonstrated. The δ-ENaC subunit is expressed in testis, ovary, pancreas, and to a lesser extent in brain and heart (pg 740, col. 1, Other Tissues). ENaC transcripts and proteins were detected in retina photoreceptors, but ENaC's role in phototransduction remains to be established.

Aberrant Expression or Activity

With respect to the limitation regarding "aberrant expression or activity", the art does not teach the objective, quantitative values to determine whether the expression or activity of the α, β and γ ENaC subunits is aberrant in the enormous genus of mammalian cell types embraced by the claims. Regulation of ENaC activity can occur at different levels, i.e. transcription, translation, translocation and degradation, as well as single-channel open probability and

conductance. ENaC subunits [α, β and γ] have been shown to be transcriptionally up-regulated by aldosterone, a low sodium diet or dexamethasone in the kidney, colon and lung, in a tissue- and subunit-specific fashion (Audige et al, Clinical Sci. 104:389-395, 2003; pg. 390, col. 1, ¶2). Using quantitative, real-time polymerase chain reaction (QT-PCR), Audige et al sought to establish whether ENaC is transcriptionally regulated in nephrotic syndrome, and whether expression of ENaC subunit mRNAs and/or protein expression correlates with the profile of urinary sodium excretion using the experimental model of PAN-induced nephrotic syndrome in the rat. Audige et al found that mRNA levels of the α, β and γ ENaC subunits fluctuated over the course of the experiment, first increasing, then decreasing, having escaped regulation by aldosterone, and that the changes in mRNA levels are not paralleled by the amount of ENaC subunit protein expression, e.g. the abundance of βENaC or γENaC protein did not significantly change throughout the study (pg 393, col. 2, Protein Expression and Discussion). Although significant sodium retention occurred from days 5 to 7 in the presence of high plasma aldosterone concentrations, ENaC mRNAs normalized and protein levels of ENaC subunits remained unchanged (pg 394, col. 1, ¶1).

Similarly, Bubien et al (J. Biol. Chem. 276(11): 8557-8566, 2001) teach that when comparing human lymphocytes from Liddle's disease patients and non-Liddle's disease patients, the Liddle's disease lymphocytes were 2.5 times more fluorescent than non-Liddle's cells when stained for expression of ENaC (pg 8562, col. 1, Immunohistochemical Analysis). However, the authors were unable to ascertain if the increased fluorescence was due to an increase in the amount of ENaC expressed on the cell surface or an increase in the number of exposed epitopes, because the exact number of epitopes and stoichiometry is not known. Bubien et al were unable to provide quantitative values of mRNA or protein expression of the α, β and γ ENaC subunits.

Diseases associated with ENaC

The physiological and pathophysiological role of ENaC in Na+ and K+ homeostasis has been clearly demonstrated in human genetic studies, and later confirmed by disruption of ENaC genes in mouse models (Kellenberger et al, pg 738, col. 2, ¶1). Mutations in the β- and γ-ENaC genes causing hyperactive channels have been found in patients with Liddle's syndrome, a hereditary form of hypertension. The role of ENaC in Na+ homeostasis was further evidenced by

the identification of mutations in ENaC causing reduced channel activity or complete loss of channel function associated with pseudohypoaldosteronism type 1 (PHA-I). The renal symptoms of this heterogeneous syndrome include hyponatremia, hypotension, and hyperkalemia and are associated with elevated plasma aldosterone and renin levels. In contrast to the kidney, the Na+ transport in the lung can be maintained efficiently by only two functional ENaC genes, i.e., the pairs αβ or αγ (Kellenberger et al, pg 739, col. 1, Lungs). In humans the contribution of α-ENaC to the clearance of fetal lung liquid at birth is still unclear.

The art is silent with respect to diseases associated with the novel amiloride-sensitive cation channel 5 and δENaC.

Gene Therapy Vectors

Applicant contemplates a broad genus of gene therapy vectors, including liposomes, viral vectors, plasmids, and a genus of undisclosed gene delivery vehicles (pg 18, line 1), wherein the agent has the known property of enhancing the delivery of the desired nucleic acid, e.g. transduction, frequency and/or broaden the serotype infectivity pattern (viral vectors) (pgs 10-11, joining ¶; pg 19). However, the claimed "efficacy" also reasonably embraces the nucleic acid sequence or elements that affect the transcriptional and/or translational regulation of the nucleic acid product. The art recognizes that gene delivery vectors include viral and non-viral vehicles, such as virosomes, liposomes, and cationic polymers. Hunziker et al (Molecular Immunol. 38: 475-484, 2001) teach that virosome preparations are technically demanding to synthesize and obtain a high level of batch-to-batch standardization because complex interactions among the components of the vaccine are hard to predict and require a thorough pre-clinical test program (pg 480, col. 2, ¶5). Similarly, Lechardeur et al (Curr. Gene Therapy 2:183-194, 2002) teach that the phospholipid membranes delineating the intracellular compartments, including the nucleosol, constitute major obstacles to the delivery of therapeutic genes. Once internalized, DNA has to escape from serial barriers, represented by endo-lysosomal entrapment, cytosolic sequestration, and nuclear exclusion. Besides these physical barriers, the DNA is also subjected to metabolic degradation, further compromising the efficiency of gene transfer (pg 183, col.s 1-2).

The Level of One of Ordinary Skill and The Level of Predictability in the Art

The level of one of ordinary skill in the clinical and gene therapy arts is considered to be high. However, sodium channels, neither known or contemplated by Applicant, that are expressed in epithelial cells are still being identified in the art and thus the association of the newly identified genes to any disease(s) is simply not known. The art teaches that "[O]ur knowledge regarding the structure and function of these [ENaC and ASIC] channels is still emerging and needs to be improved (Kellenberger et al; pg 760, col. 1, Perspectives). Inherited human diseases cause by the ENaC family members hINAC and ASICs have not been identified to date (Kellenberger et al; pg 760, col. 2, last ¶). Even within the contemplated ENaC α, β and γ genes, the breadth of disease states and symptoms thereof caused by aberrant expression or activity of these genes is not fully described in the art because the art has not identified quantitative measurements to objectively determine what is "aberrant", especially with respect to the enormous genus of mammalian cell types embraced by the claims. Similarly, the multitude of variables required for the synthesis of a therapeutically effective gene therapy vector is complex and non-obvious. Thus, one of ordinary skill in the art would reasonably conclude a significant degree of unpredictability regarding an artisan to *a priori* select an agent that inhibits or treats one or more symptoms of an enormous genus of diseases that are associated with aberrant expression or activity of amiloride-sensitive epithelial sodium channel proteins αENaC, βENaC and γENaC, or an agent that enhances the efficacy of an enormous genus of structurally and functionally distinct gene therapy vectors.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The method comprises the step of selecting one or more agents which inhibit or treat one or more symptoms of a disease which is associated with aberrant expression or activity of epithelial sodium channels. Thus, the claims reasonably embrace an enormous genus of etiologically and pathologically distinct diseases having an essentially infinite degree of "association with" the activity or expression of a genus of epithelial sodium channels, wherein said activity or expression is determined to be "aberrant".

The elected embodiment of the agent is an antibiotic. However, there is no disclosure in the specification teaching the nexus between an antibiotic and the treatment of a disease caused

by aberrant expression of amiloride-sensitive epithelial sodium channel proteins αENaC, βENaC and γENaC as opposed to the use of an antibiotic to treat any other disease symptom not caused by aberrant expression of amiloride-sensitive epithelial sodium channel proteins αENaC, βENaC and γENaC. The specification broadly discloses that ENaC activity may be inhibited by... altering the trafficking and processing of molecules through intracellular compartments, including without limitation proteasomes, endosomes, and trans-Golgi, and/or through the cytosol, e.g., via cytoskeletal components such as microtubules and microfilaments (pg 17, lines 1-8). Applicant further contemplates that altering ENaC activity may be accomplished by decreasing ENaC transcription via direct interaction with the promoter of one or more ENaC subunits, e.g. methylation or a repressor (pg 17, lines 10-21). These contemplations do not provide specific guidance to the artisan directly leading the artisan to select an antibiotic.

Furthermore, the specification fails to disclose the quantitative values and relationships linking the claimed limitations. There is no definition by which the expression or activity of the genus of claimed sodium channels are to be considered "aberrant", no guidance or direction to the artisan as to the degree by which a disease, including those contemplated by Applicant (pg 9, lines 9-10), is associated with changes in expression or activity of an epithelial sodium channel, and no definition of the term "symptoms of a disease". Not all symptoms of a disease caused by aberrant expression of amiloride-sensitive epithelial sodium channel proteins αENaC, βENaC and γENaC are treatable by the administration of an antibiotic, and the specification fails to disclose the necessary guidance to the artisan for choosing an antibiotic over some other agent.

The method also comprises the step of selecting an agent that enhances the efficacy of a gene therapy vector in mammalian cells. Applicant contemplates the gene therapy vector may be a liposome, a viral vector, a plasmid, or one of a genus of undisclosed gene delivery vehicles (pg 18, line 1). But as discussed above, the art recognizes a multitude of structurally and functionally distinct gene therapy vectors. However, the specification fails to disclose or define the phrase "efficacy of a gene therapy vector". Furthermore, there is no disclosure in the specification teaching the nexus between an antibiotic and how the antibiotic alters expression or activity of amiloride-sensitive epithelial sodium channel proteins αENaC, βENaC and γENaC.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Given the absence of definitions and the lack of disclosure, the specification fails to provide the necessary guidance and direction so that an artisan would know *a priori* that a particular agent has the required inherent property of inhibiting or treating one or more symptoms of an enormous genus of etiologically and pathologically distinct diseases, wherein the disease is not actually required to be caused by aberrant activity of epithelial sodium channels, the relationship between a given disease and an epithelial sodium channel, and the necessary quantitative values of epithelial sodium channel expression and/or activity so as to determine differences in expression and/or activity to be "aberrant", or what property of an enormous genus of structurally and functionally distinct gene therapy vectors must be enhanced by the agent, so as to perform the method steps as claimed. The artisan must first select an agent and then test the agent to determine whether or not it possesses all of the recited limitations before proceeding with the method step of contacting a mammalian cell.

The instant portion of the invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech Inc v. Novo NordiskA/S* 42 USPQ2d 1001, at 1005). The claimed method steps of selecting one or more agents *a priori* having the recited properties are such "germs of an idea".

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Exparte Maizel.* In the instant case, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. **Claims 1-7, 13, 15-16, 20 and 23 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, Claims 1-2 recite the broad recitation epithelial sodium channels, and the claim also recites "(ENaC)", which is the narrower statement of the limitation.

The specification discloses prior art to identify the claimed subject matter (pg 1, line 24; Stutts et al, J. Biol. Chem. 272(22):14037-14040, 1997; Donaldson et al, J. Biol. Chem. 277(10):8338-8345, 2002 *of record), wherein the art teaches that ENaC is an acronym for amiloride-sensitive epithelial sodium channel, wherein the art recognizes that ENaC is composed of α, β and γ subunits.

The Examiner respectfully suggests amending the claims to read "...of amiloride-sensitive epithelial sodium channel proteins αENaC, βENaC and γENaC".

Claims 1 and 2 recite the methods to comprise the step of selecting an agent that "enhances the efficacy of a gene therapy vector" in mammalian cells. The term "efficacy" in the claims is a relative term which renders the claims indefinite. The term "efficacy" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant contemplates the gene therapy vector may be a liposome, a viral vector, a plasmid, or one of a genus of undisclosed gene delivery vehicles (pg 18, line 1). But as discussed above, the art recognizes a multitude of structurally and functionally distinct gene therapy vectors. As such, the metes and bounds of the recited limitation are indefinite because an artisan would not know *a priori* what effect is encompassed by the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. **Claims 1-5, 7, 15-16, 20 and 23 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Yalkinoglu et al (Int. J. Cancer 45(6): 1195-1203, 1990, Abstract only), Bohl et al (Blood 92(5):1512-1517, 1998) or Schwarzbach et al (Int. J. Oncology 20: 1211-1218, 2002).

The claims are drawn to a method to identify one or more agents with dual therapeutic activity.

Yalkinoglu et al teach the administration of adriamycin (also known as doxorubicin) and adeno-associated virus 2 on Chinese hamster ovary (CHO) cells. Bohl et al teach the administration of the antibiotic doxycycline and the gene therapy vector AAV (pg 1513) to mammalian cells, specifically human myocytes (pg 1513, col. 1, Human cultures), wherein the doxycycline induces the expression of the marker gene erythropoietin (EPO) (pg 1513, Results). Schwarzbach et al teach the method step of selecting the antibiotic doxorubicin (pg 1212, Materials and Methods), and administering the doxorubicin and the gene therapy vector AAV-2 to human cells, wherein the administration of doxorubicin enhanced the effect of the AAV-2, namely increased cell killing (e.g., pg 1213, Figure 1).

The cited art does not teach the antibiotic to treat one or more symptoms of a disease which is associated with aberrant expression or activity of an epithelial sodium channel. However, absent evidence to the contrary, the antibiotic inherently possesses the recited ability because, for example, doxorubicin is an art-recognized antibiotic and is disclosed in the instant specification to possess the recited functional limitations.

The cited art does not teach the mammalian cells to have aberrant expression or activity of epithelial sodium channels. However, the specification fails to disclose or define the quantitative values by which the expression or activity of the claimed sodium channels are to be considered "aberrant". Thus, absent evidence to the contrary, the cells of the cited have some degree of aberrant expression or activity of the claimed sodium channels.

The cited art does not teach that the antibiotics modulate transcription of one or more molecules that regulate ENaC transcription. However, absent evidence to the contrary, the antibiotics inherently possess such modulatory abilities as per the disclosure of the instant

specification (pg 5, line 22), as there is nothing of record to distinguish the doxorubicin of Schwarzbach et al with the doxorubicin of the instant application, for example.

It would have been obvious to one of ordinary skill in the art to modify the methods of Yalkinoglu et al, Bohl et al and/or Schwarzbach et al to identify one or more agents with dual therapeutic activity with a reasonable chance of success because the cited prior art have performed the recited method steps, have observed phenotypic effects on the gene therapy vector and/or cells caused by the administration the selected agent, and thus have effectively identified an agent with dual therapeutic activity.

An artisan would be motivated to modify the methods of the cited prior art because the art did not directly ascertain the nature and degree of epithelial sodium channel expression or activity in the target mammalian cells, nor measure changes in epithelial sodium channel expression or activity as a response to the administration of the agent and viral vector to the target mammalian cells.

Thus, the invention as a whole is *prima facie* obvious.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Q. JANICE LI, M.D.
PRIMARY EXAMINER